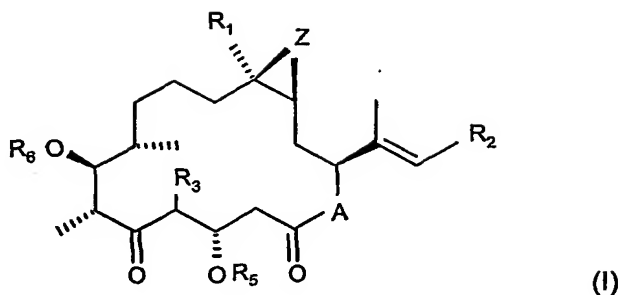


What is claimed is:

## 1. An epothilone of formula I



wherein

A represents O or NR<sub>7</sub>,

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino,

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom,

R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl,

Z is O or a bond,

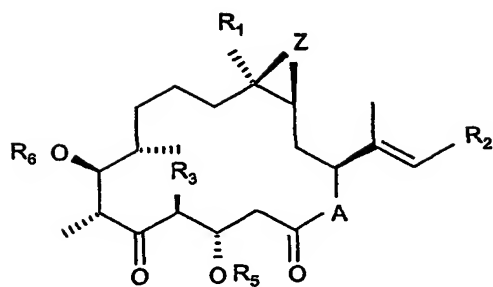
under the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, and

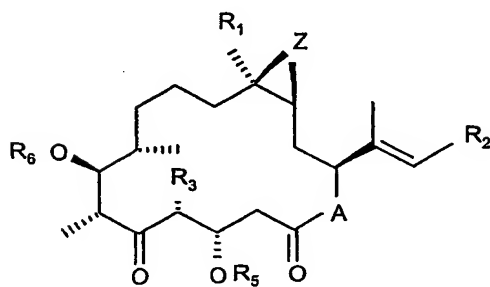
when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

or a salt thereof.

## 2. An epothilone of formula Ia or Ib



(1a)



(1b)

wherein

A represents O or NR<sub>7</sub>,

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino,

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom,

R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl,

Z is O or a bond,

under the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

or a salt thereof.

3. The epothilone of formula I according to claim 1 or of formula Ia or Ib according to claim 2, wherein

A represents O or NR<sub>7</sub>,

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino,

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, benzoxazolyl or benzoimidazolyl, which in each case is substituted or unsubstituted,

R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl,

Z is O or a bond,

under the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

or a salt thereof.

4. The epothilone of formula I according to claim 1 or of formula Ia or Ib according to claim 2, wherein

A represents O or NR<sub>7</sub>,

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, which in each case is substituted or unsubstituted,

R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl,

Z is O or a bond,

under the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

or a salt thereof.

5. The epothilone of formula I according to claim 1 or of formula Ia or Ib according to claim 2, wherein

A represents O,

R<sub>1</sub> is hydrogen or lower alkyl,

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl-benzothiazolyl,

R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

Z is O or a bond,

under the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

6. The epothilone of formula I according to claim 1 or of formula Ia or Ib according to claim 2, wherein

A represents O,

R<sub>1</sub> is hydrogen or lower alkyl,

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl-benzothiazolyl,

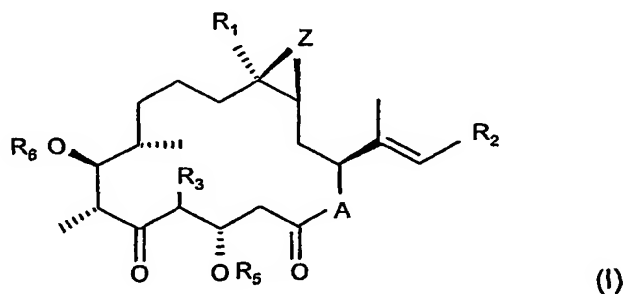
R<sub>3</sub> represents methyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

Z is O or a bond,

under the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

7. A pharmaceutical composition, comprising an epothilone of formula I or of formula Ia or Ib, or a pharmaceutically acceptable salt thereof, provided that salt-forming groups are present, according to one of claims 1 to 6, and one or more pharmaceutically acceptable carriers.
8. Use of an epothilone of formula I or of formula Ia or Ib according to one of claims 1 to 6 for the treatment of a tumour disease.
9. Use of an epothilone of formula I or of formula Ia or Ib according to one of claims 1 to 6 for the preparation of a pharmaceutical product for the treatment of a tumour disease.
10. A method for treatment of warm-blooded animals, including humans, in which an therapeutically effective amount of an epothilone of the formula I or of formula Ia or Ib according to any one of claims 1 to 6 or a pharmaceutically acceptable salt of such a compound is administered to a warm-blooded animal suffering from a tumour disease.
11. A process for the preparation of an epothilone of formula I,



wherein

A represents O or NR<sub>7</sub>,

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom,

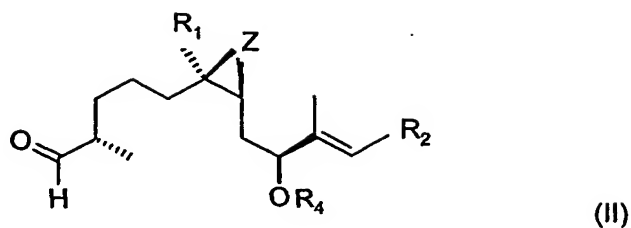
R<sub>3</sub> represents hydrogen or lower alkyl,

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

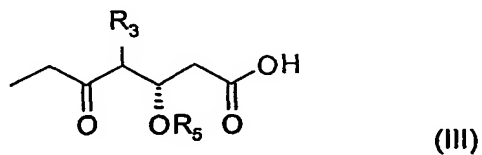
R<sub>7</sub> is hydrogen or lower alkyl,

Z is O or a bond,

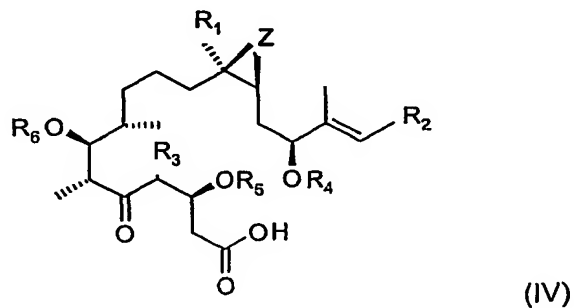
wherein an aldehyde of formula II



wherein R<sub>1</sub>, R<sub>2</sub> and Z have the meanings as provided above for a compound of formula I and R<sub>4</sub> is a protecting group, is reacted in a first step with an ethylketone of formula III,



wherein R<sub>5</sub> is H or a protecting group different or identical to R<sub>4</sub> and R<sub>3</sub> has the meaning as provided above for a compound of formula I, to provide the aldol of formula IV,



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and Z have the meanings as provided above for a compound of formula I, R<sub>4</sub> a protecting group, R<sub>5</sub> is H or a protecting group different or identical to R<sub>4</sub> and R<sub>6</sub> is hydrogen,

which aldol of formula IV is reacted in a second step with a reagent capable to introduce a protecting group which is different or identical to  $R_4$  furnishing a carboxylic acid of formula IV,

wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $Z$  have the meanings as provided above for a compound of formula I,  $R_4$  a protecting group and  $R_5$  is H or  $R_5$  and  $R_6$  are protecting groups different or identical to  $R_4$ ,

which carboxylic acid of formula IV is reacted in a third step with a reagent capable to remove the protecting group  $R_4$  under conditions which do not result in the removal of the protecting groups  $R_5$  and  $R_6$  providing a carboxylic acid of formula IV,

wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $Z$  have the meanings as provided above for a compound of formula I,  $R_4$  is hydrogen and  $R_5$  is H or  $R_5$  is H or  $R_5$  and  $R_6$  are protecting groups,

which carboxylic acid of formula IV in a fourth step is subject of a macrolactonisation reaction providing the epothilone of formula I,

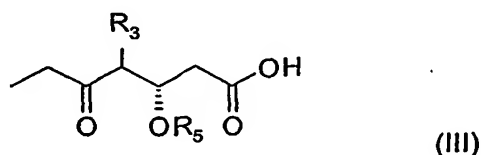
wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $Z$  have the meanings as provided above for a compound of formula I,  $A$  is O and  $R_5$  is H or  $R_5$  and  $R_6$  are protecting groups,

which epothilone of formula I is reacted in a fifth step with a reagent capable to remove the protecting groups  $R_5$  and  $R_6$  furnishing an epothilone of formula I,

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$  and  $Z$  have the meanings as provided above for a compound of formula I and  $A$  is O,

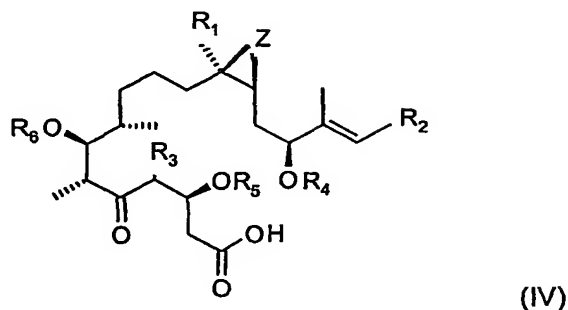
which epothilone of formula I is, optionally, further transformed into an epothilone of formula I wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$  and  $Z$  have the meanings as provided above for a compound of formula I and  $A$  is  $NR_7$ , wherein  $R_7$  is hydrogen or lower alkyl.

12. An ethylketone of formula III,



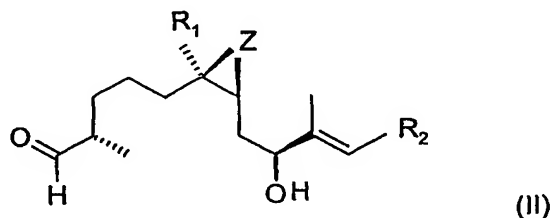
wherein  $R_3$  has the meaning as provided above for a compound of formula I and  $R_5$  is hydrogen or a protecting group.

13. An aldol of formula IV,



$R_1$  is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, lower acyl amino,  $R_2$  is unsubstituted or substituted heteroaryl,  $R_3$  represents hydrogen or lower alkyl,  $R_4$  is hydrogen or a protecting group,  $R_5$  is a protecting group different or identical to  $R_4$ ,  $R_6$  is hydrogen or a protecting group different or identical to  $R_4$ , and  $Z$  is O or a bond.

14. A process for the preparation of an aldehyde of formula II



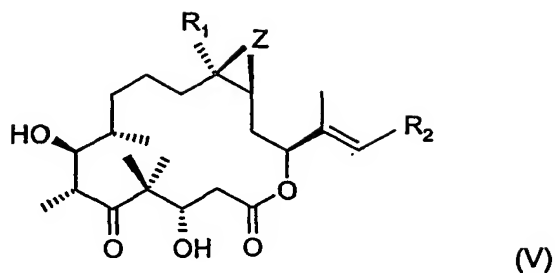
wherein

$R_1$  is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, lower acyl amino,  $R_2$  is unsubstituted or substituted heteroaryl,



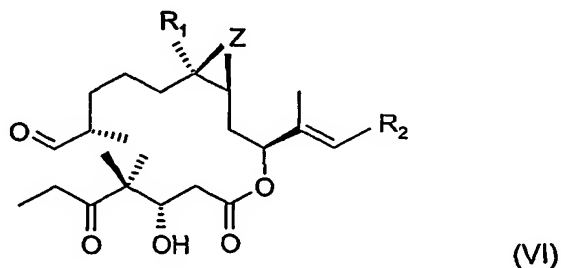
Z is O or a bond,

wherein an epothilone of formula V



wherein the radicals  $R_1$ ,  $R_2$  and Z have the meanings as provided for a compound of formula II above,

is first reacted with a reagent effecting a retro-aldol reaction furnishing an ester of formula VI



wherein the radicals  $R_1$ ,  $R_2$  and Z have the meanings as provided for a compound of formula II above,

which ester is hydrolized in a second step into its components, 4,4-dimethyl-3-hydroxy-5-oxo-heptanoic acid and the aldehyde of formula II as defined above.

15. A method of separating C4-desmethyl-epothilone B from epothilone G2, which is characterised by chromatography on a Chiralpak-AD column with an eluant containing a lower alkane and a lower alkanol.

16. A process for the production of C4-desmethyl-epothilone B, which comprises the steps of  
a) concentrating epothilones in a culture medium for the biotechnological preparation of epothilones, which medium contains a microorganism suitable for the preparation of epothilones, water and other suitable customary constituents of culture media, whereby a

cyclodextrin or a cyclodextrin derivative is added to the medium, or a mixture of two or more of these compounds;

- b) separating epothilones from one another, which is characterised by chromatography on a reversed-phase column with an eluant containing a lower alkylcyanide, wherein chromatography is carried out on column material charged with hydrocarbon chains, and an eluant containing a lower alkylnitrile is used; and wherein, if desired, further working up steps and purification steps are possible; and
- c) finally separating C4-desmethyl-epothilone B from epothilone G2, by chromatography on a Chiralpak-AD column with an eluant containing a lower alkane, and a lower alkanol.